REMARKS

Claims 1-7, 14-32, 50 and 52-54 were pending in the subject application. Applicants have hereinabove amended claims 5, 14, 23 and 50, and added new claim 55-72. Accordingly, claims 1-7, 14-32, 50 and 52-72 are currently pending in the subject application.

Information Disclosure Statement

In Section 2 of the December 13, 2001 Office Action, the Examiner noted that an IDS was filed on June 29, 2001, but indicated that the form PTO-1449 or the references could not be found.

In response, applicants submit as **Exhibit 1** a copy of the form PTO-1449 and as **Exhibit 2** a copy of the stamped postcard receipt indicating that the U.S. Patent Office received the Information Disclosure Statement, including form PTO-1449 and 87 references on June 29, 2001. The form PTO-1449 and each of the references were clearly marked with the subject application's Serial No. and filing date. If the references received by the U.S. Patent Office on June 29, 2001 have not yet been forwarded to the Examiner by the Office personnel, applicants request that the Examiner notify applicants' attorney by telephone call at the number provided below and applicants' will be happy to hand deliver a courtesy copy of the references directly to the Examiner.

Objection to Claims

The Examiner objected to claims 2-4 alleging they are substantial duplicates of claim 1, and also objected to claims 6 and 7 alleging they are substantial duplicates of claim 5. The Examiner did not see a distinction between the limitations

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"substantially free of the A polymorph" and "substantially homogeneous".

In response, applicants respectfully point out that being "substantially free of the A polymorph" is not necessarily synonymous with being "substantially homogeneous". Applicants respectfully request that the Examiner reconsider these term and withdraw the objection.

Rejection under 35 U.S.C. § 112, second paragraph - claims 5-7

In Section 5 of the December 13, 2001 Office Action the Examiner rejected claims 5-7 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The three rejected claims are compositions containing polymorph B and all lack a carrier.

In response, applicants have amended claims 5-7 to recite a carrier as suggested by the Examiner. Accordingly, the rejection under 35 U.S.C. § 112, second paragraph is moot.

Rejection under 35 U.S.C. § 112, second paragraph - claims 14 and 17-23

In Section 6 of the December 13, 2001 Office Action the Examiner rejected claims 14 and 17-23 under 35 U.S.C. 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner alleged that the phrase "a hyperproliferative disorder" is indefinite, noting, however, that from the dependent claims, it is clear that this disorder includes solid tumors. The

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Examiner questioned whether leukemias are also covered, whether psoriasis is "a hyperproliferative disorder", and whether hirsutism be covered.

In response, applicants respectfully submit that the term "hyperproliferative disorder" would be readily understood by one of skill in the art. For example, "proliferation" is defined by Stedman's Medical Dictionary, 27th Edition, to mean "growth and reproduction of similar cells." The prefix "hyper-" is defined by the same dictionary as meaning "excessive, above normal." A copy of the relevant portions of the dictionary are attached is **Exhibit 3**. Thus, the term "hyperproliferative disorder" would be readily understood by one of skill in the art to mean a disorder where there is abnormal cell growth. To advance prosecution of the subject application, applicants have amended the claims to recite "abnormal cell growth" instead of "hyperproliferative disorder", which terms applicants contend are synonymous. Applicants will use the term "abnormal cell growth" because this term is explicitly defined in the subject application on page 23, line 25 to page 24, line 7, and exemplified throughout the subject specification.

Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. § 112, first paragraph - claims 14 and 16-22

In Section 7 of the December 13, 2001 Office Action, the Examiner rejected claims 14 and 16-22 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which

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was not described in the specification in such a way as to reasonably enable one skilled in the relevant art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleged that applicants are not enabled for treatment of "a hyperproliferative disorder" generally. The Examiner cited *In re Buting* 163 USPQ 689, for the preposition that evidence involving a single compound and two type of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of *a class of several compounds*. The Examiner also cited Draetta (Ann. Reports Med. Chem.), final sentence on page 246, for the quote, "[A]lthough many still think about the need for a magic bullet as a cure for all cancers, our knowledge of the molecular mechanism underlying this disease make the prospect of developing such a universal cure very unlikely." The Examiner *did acknowledge that advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer.*

In response, applicants point out that the rejected claims 14 and 16-22 are all directed to a specific compound for the treatment of specific types of cancer. The Examiner's citation of *In re Buting* 163 USPQ 689 and Draetta is misplaced, therefore. Applicants specification, on the very first page, states that the specific compound, a polymorph of which applicants are now claiming, is known to be an inhibitor of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR), and is therefore useful for the treatment of associated diseases. The diseases which are known to fall

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within this class are described, for example, on pages 24-29 on the subject specification.

Importantly, Phase I and II Clinical Studies are described on pages 50 to 53 of the subject specification for non-small cell lung cancer, head and neck cancer, refractory ovarian cancer, colorectal cancer, renal carcinoma. Of note is that the Examiner has rejected claim 16, which recites this group of cancers. This rejection of claim 16, applicants contend, is clearly improper.

All of the cancers of the Clinical Trials are EGFR positive tumor types. As noted in the description of the Clinical Trials on page 52, lines 32-35, other EGFR positive tumor types have been documented to be affected by the specific compound. Therefore, applicants have enabled the treatment of any disease by the inhibition of the erbB family of oncogenic and protooncogenic protein tyrosine kinases, such as epidermal growth factor receptor (EGFR).

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. 112, first paragraph - claim 50

In Section 8 of the December 13, 2001 Office Action, the Examiner rejected claim 50 under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner alleged that despite intensive efforts,

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pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of proliferative diseases generally. The Examiner stated that under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609, and no such evidence has been presented in this case. The Examiner further alleged that the failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ 2nd 1001, 1006.

In response, applicants have amended claim 50 to recite prophylaxis against the development of basal or squamous cell carcinoma of the skin. Prophylaxis against the development can be readily practiced by anyone skilled in the art and does not require prevention. As the Examiner will appreciate, because the recited compound is known to inhibit EGFR, and basal and squamous cell carcinomas are EGFR positive, it is reasonable to expect a prophylactic effect against these carcinomas during early stages.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 50, as amended, under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. 102(e)

In Section 9 of the December 13, 2001 Office Action, the Examiner rejected claims 1-7, 14-23, 50, and 52-54 under 35 U.S.C. 102(e) as allegedly anticipated by U.S. Patent No. 5,747,498 to Schnur ("the '498 patent"). The Examiner alleged that the reference teaches the synthesis and

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crystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride in Example 20, lines 30-49, column 22. The Examiner acknowledged that applicants have amply characterized their claimed material, polymorph B, but alleged that there is no side-by-side comparison to the material taught by the reference. The Examiner noted that applicants state that polymorph B is the more stable form. The Examiner question whether the material made by Schnur ('498) is polymorph A, whether earlier workers also found the more stable form, and whether the material prepared by Schnur ('498) could contain some or substantial amounts of polymorph B.

In response, applicants respectfully submit that it is improper to base an anticipation rejection on what someone could have possibly prepared. The word "polymorph" does not appear in the '498 patent. The process of Example 20 of the '498 patent is not the same as the process described by the subject application for preparing claimed polymorph B.

Therefore, the anticipation rejection is improper at least because all of the recited elements of applicants' claims are not found in the '498 patent. Assuming, arguendo, that the Examiner is relying on an inherency theory, applicants respectfully point out that inherency cannot be predicated on mere possibilities.

Accordingly, the rejection under 35 U.S.C. § 102 should be withdrawn.

Rejection under 35 U.S.C. 103(a)

In Section 10 of the December 13, 2001 Office Action, the

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Examiner rejected claims 24-32 under 35 U.S.C. § 103(a) as allegedly unpatentable over Schnur ('498). The Examiner alleged that the reference teaches crystallization of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride from chloroform and ether. The Applicants claim crystallization from water and alcohol. The Examiner alleged that the difference between the claimed and taught processes is the solvent employed, and changes in solvent are a matter of routine experimentation to the process chemist trying safer and less flammable solvents for the pilot plant. The Examiner quoted the Board of Patent Appeals and Interferences in *Ex parte Goldschmidt*, 123 USPQ 41 "It is our opinion that is does not amount to invention for the skilled chemist...to determine...which specific organic solvent is most suitable".

In response, applicants respectfully point out that the rejection fails to explain how, merely from the disclosure of the '498 patent, one would be motivated to 1) try the specific combination of water and alcohol, and 2) have a reasonable expectation of the success of this combination. In fact, the rejection even fails to point out where in the '498 patent a combination of solvents of water and alcohol are taught or suggested. Even if all of these shortcomings of the rejection could be addressed by the proffered "routine experimentation" theory, how one would arrive at a process for preparing polymorph B, as recited in claims 24-32, is also not explained in the rejection.

Accordingly, the rejection under 35 U.S.C. § 103 should be withdrawn.

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Conclusion

In view of the amendments and remarks hereinabove, applicants maintain that the cited reference does not teach or suggest applicants' claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejections and objection set forth in the December 13, 2001 Office Action and earnestly solicit allowance of the pending claims.

No fee, other than the enclosed $920.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents
Washington, D.C. 20231.

Gary J. Gershik 6/13/02

John P. White Date
Reg. No. 28,678
Gary J. Gershik
Reg. No. 39,992

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TITLE WITH REVISION SHOWN

STABLE POLYMORPH ON N-(3-ETHYNYLPHENYL~~AMINO~~)-6,7-BIS (2-METHOXYETHOXY)-4-QUINAZOLINAMINE HYDROCHLORIDE, METHODS OF PRODUCTION, AND PHARMACEUTICAL USES THEREOF

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CLAIM SET WITH REVISION SHOWN

1. A substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14, and 26.91.

2. The polymorph of claim 1, characterized by the X-ray powder diffraction pattern shown in Figure 3.

3. A crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, which is substantially free of the A polymorph.

4. The polymorph of claim 3, characterized by the X-ray powder diffraction pattern shown in Figure 3.

5. (Amended) A composition comprising a substantially homogeneous crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14

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and, 26.91, and a carrier.

6. The composition of claim 5, wherein the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

7. The composition of claim 5, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

14. (Amended) A method of treating ~~a hyperproliferative disorder~~ abnormal cell growth in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 1.

15. The method of claim 14, wherein the method is for the treatment of a cancer selected from brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.

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16. The method of claim 14, wherein the method of for the treatment of a cancer selected from non-small cell lung cancer (NSCLC), refractory ovarian cancer, head and neck cancer, colorectal cancer and renal cancer.

17. The method of claim 14, wherein the therapeutically effective amount is from about 0.001 to about 100 mg/kg/day.

18. The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 35 mg/kg/day.

19. The method of claim 14, wherein the therapeutically effective amount is from about 1 to about 7000 mg/day.

20. The method of claim 19, wherein the therapeutically effective amount is from about 5 to about 2500 mg/day.

21. The method of claim 20, wherein the therapeutically effective amount is from about 5 to about 200 mg/day.

22. The method of claim 21, wherein the therapeutically effective amount is from about 25 to about 200 mg/day.

23. (Amended) A method for the treatment of ~~a hyperproliferative disorder~~ <u>abnormal cell growth</u> in a mammal which comprises administering to said mammal a therapeutically effective amount of the polymorph of claim 1 in combination with an anti-tumor agent selected from the group consisting of a mitotic inhibitor, an alkylating agent, an anti-metabolite, an intercalating antibiotic, a growth factor inhibitor, a cell cycle

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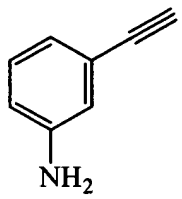
inhibitor, an enzyme, a topoisomerase inhibitor, a biological response modifier, an anti-hormone, and an anti-androgen.

24. A method of preparing a crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride designated the B polymorph which comprises the step of recrystallizing -(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in a solvent comprising alcohol.

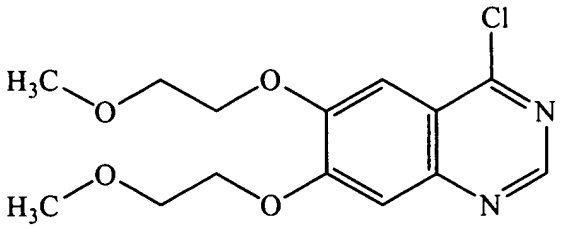
25. The method of claim 24, wherein the solvent further comprises water.

26. The method of claim 24, wherein N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride is prepared by coupling a compound of formula 6



6

with a compound of formula 4



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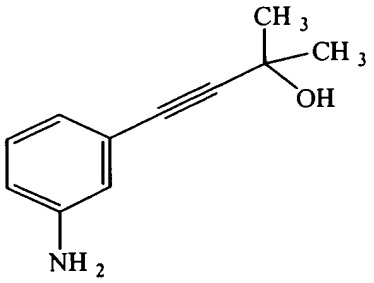
27. The method of claim 26, wherein said compound of formula 6 is prepared by reacting a compound of formula 5



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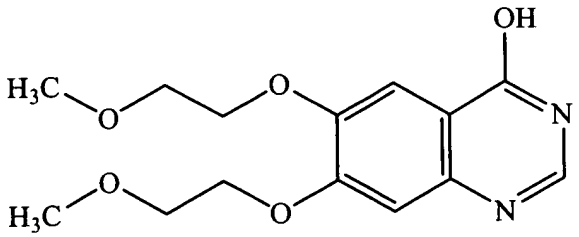
in a suspension of metal alkali and solvent and with heating.

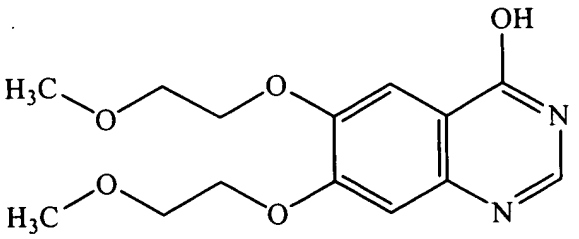
28. The method of claim 26, wherein said compound of formula 4 is prepared by chlorinating a compound of formula 3



3.

29. A method for the production of the polymorph B of claim 1 comprising the steps of:

a) substitution chlorination of starting quinazolinamine compound of formula 3



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having an hydroxyl group, to provide a compound of formula 4

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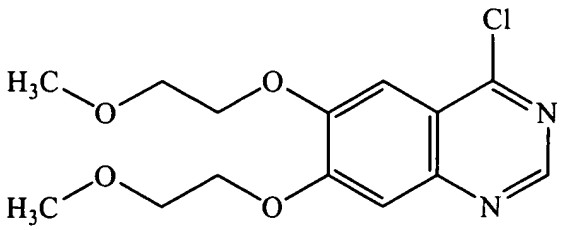

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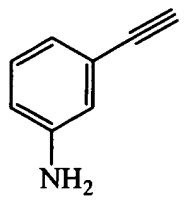
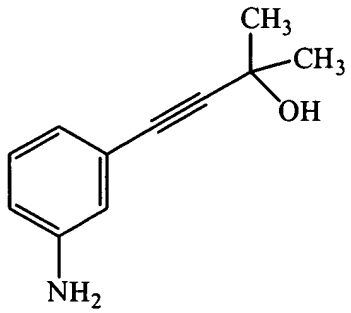
by reaction thereof in a solvent mixture of thionyl chloride, methylene chloride and dimethylformamide,

b) preparation of a compound of formula 6



6

in situ from starting material of compound of formula 5



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by reaction of the latter in a suspension of metal alkali and solvent and with heating;

c) reaction of the compound of formula 6 in situ with the compound of formula 4 wherein the compound of formula 6 replaces the chlorine in the compound of formula 4 to give the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride;

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d) recrystallizing the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride, in alcohol, into the polymorph B form.

30. The method of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium hydroxide.

31. The method of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous sodium bicarbonate.

32. The method of claim 29, wherein the substitution chlorination is quenched in the presence of aqueous potassium hydroxide, aqueous potassium bicarbonate, aqueous potassium carbonate, aqueous sodium carbonate, or a mixture thereof.

50. (Amended) A method for ~~the chemoprevention~~ prophylaxis against the development of basal or squamous cell carcinoma of the skin in areas exposed to the sun or in persons of high risk to said carcinoma, said method comprising administering to said persons a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms, so as to thereby result in prophylaxis against the development of basal or squamous cell carcinoma of the skin.

52. A method of making a composition which composition comprises substantially homogeneous crystalline polymorph

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of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91, comprising admixing the crystalline polymorph of claim 1 with a carrier.

53. The method of claim 52, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

54. The method of claim 52, wherein the carrier is a pharmaceutically acceptable carrier.

55. (New) A composition comprising a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph that exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately 6.26, 12.48, 13.39, 16.96, 20.20, 21.10, 22.98, 24.46, 25.14 and, 26.91 in a weight % of the B polymorph relative to the A polymorph which is at least 70%.

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56. (New) The composition of claim 55, wherein the B polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta at approximately:

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

57. (New) The composition of claim 55, wherein the N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the polymorph B form is characterized by the X-ray powder diffraction pattern shown in Figure 3.

58. (New) A pharmaceutical composition which comprises a therapeutically effective amount of the polymorph of claim 1 and a pharmaceutically acceptable carrier.

59. (New) The pharmaceutical composition of claim 58, wherein said composition is adapted for oral administration.

60. (New) The pharmaceutical composition of claim 59, wherein the pharmaceutical composition is in the form of a tablet.

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61. (New) A method for the production of a crystalline polymorph of the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine designated the B polymorph by recrystallization comprising the steps of:

e) heating to reflux alcohol, water and the hydrochloride salt of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine so as to form a solution;

f) cooling the solution to between about 65 and 70 °C;

g) clarifying the solution; and

h) precipitating polymorph B by further cooling the clarified solution.

62. (New) A composition comprising a substantially homogeneous crystalline polymorph of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine hydrochloride in the form of polymorph B, which is characterized by the following peaks:

Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range # 1 - Coupled 3.000 to. 40.040 StepSize: 0.040 StepTime 1.00

Smoothing Width: 0.300 Threshold: 1.0

d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)	d(A)	I(rel)
14.11826	100.0	5.01567	2.5	3.86656	4.8	3.23688	0.9	2.74020	1.7
11.23947	3.2	4.87215	0.7	3.76849	2.3	3.16755	1.5	2.69265	1.7
9.25019	3.9	4.72882	1.5	3.71927	3.0	3.11673	4.3	2.58169	1.5
7.74623	1.5	4.57666	1.0	3.63632	6.8	3.07644	1.4	2.51043	0.8
7.08519	6.4	4.39330	14.4	3.53967	10.0	2.99596	2.1	2.47356	1.0
6.60941	9.6	4.28038	4.2	3.47448	3.7	2.95049	0.9	2.43974	0.6
5.98828	2.1	4.20645	14.4	3.43610	3.9	2.89151	1.6	2.41068	1.1
5.63253	2.9	4.06007	4.7	3.35732	2.8	2.83992	2.2	2.38755	1.4
5.22369	5.5	3.95667	4.5	3.31029	5.6	2.81037	2.4	2.35914	1.7

or,

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Polymorph B

Anode: Cu - Wavelength 1 1.54056 Wavelength 2: 1.54439 (Rel Intensity:0.500)

Range# 1 - Coupled: 3.000 to 40.040 StepSize 0.040 StepTime: 1.00

Smothing Width:0.300 Threshold: 1.0

2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)	2-Theta	I(rel)
6.255	100.0	17.668	2.5	22.982	4.8	27.534	0.9	32.652	1.7
7.860	3.2	18.193	0.7	23.589	2.3	28.148	1.5	33.245	1.7
9.553	3.9	18.749	1.5	23.906	3.0	28.617	4.3	34.719	1.5
11.414	1.5	19.379	1.0	24.459	6.8	29.000	1.4	35.737	0.8
12.483	6.4	20.196	14.4	25.138	10.0	29.797	2.1	36.288	1.0
13.385	9.6	20.734	4.2	25.617	3.7	30.267	0.9	36.809	0.6
14.781	2.1	21.103	14.4	25.908	3.9	30.900	1.6	37.269	1.1
15.720	2.9	21.873	4.7	26.527	2.8	31.475	2.2	37.643	1.4
16.959	5.5	22.452	4.5	26.911	5.6	31.815	2.4	38.114	1.7

63. (New) A method of inducing differentiation of tumor cells in a tumor comprising contacting the cells with an effective amount of the compound of claim 1, or a composition of claims 3 or 6 so as to thereby differentiate the tumor cells.

64. (New) A method for the treatment of NSCLC (non small cell lung cancer), pediatric malignancies, cervical and other tumors caused or promoted by human papilloma virus (HPV), melanoma, Barrett's esophagus (pre-malignant syndrome), adrenal and skin cancers and auto immune, neoplastic cutaneous diseases and atherosclerosis in a mammal comprising administering to said mammal a therapeutically effective amount of a pharmaceutical composition comprised of at least one of N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, and pharmaceutically acceptable salts thereof in anhydrous and hydrate forms.

65. (New) The method of claim 64, wherein the treatment further comprises a palliative or neo-adjuvant/adjuvant monotherapy.

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66. (New) The method of claim 64, wherein the treatment further comprises blocking epidermal growth factor receptors (EGFR).

67. (New) The method of claim 64, for use in treatment of tumors that express EGFRvIII.

68. (New) The method of claim 64, wherein the treatment further comprises a combination with any of chemotherapy and immunotherapy

69. (New) The method of claim 64, wherein the treatment further comprises, treatment with either or both anti-EGFR and anti-EGF antibodies.

70. (New) The method of claim 64, wherein the treatment further comprises a further administration to said mammal of a member of the group consisting of inhibitors of MMP (matrix-metallo-proteinase), VEGFR (vascular endothelial growth factor receptor), farnesyl transferase, $CTLA_4$.(cytotoxic T-lymphocyte antigen 4) and erbB2, MAb to VEGFr, rhuMAb-VEGF, erbB2 MAb and avb3 Mab.

71. (New) The method of claim 64, wherein the pharmaceutical compounds are used as radiation sensitizers for cancer treatment or in combination with anti-hormonal therapies.

72. (New) The method of claim 64, wherein the pharmaceutical compounds are used for the inhibition of tumor growth in humans in a regimen with radiation treatment.

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